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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/904,877	07/12/2001	Avi Ashkenazi	GEN:1618P2C27	4450

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EXAMINER	
SPECTOR, LORRAINE	

ART UNIT	PAPER NUMBER
1647	13

DATE MAILED: 04/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 39-51 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 39-51 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

Part III: Detailed Office Action

Claims 39-51 are pending and under consideration.

The pending claims are directed to PRO326, SEQ ID NO: 294, which is encoded by SEQ ID NO: 293, DNA 37140-1234, deposited as ATCC 209489.

Priority determination:

Based upon the lack of utility and enablement of the claimed subject matter, priority is granted only to the instant filing date, 7/17/01.

Should the applicant disagree with the examiner's factual determination above, it is incumbent upon the applicant to provide the serial number and specific page number(s) of any parent application filed prior to 7/17/01 which specifically supports the particular claim limitation for each and every claim limitation in all the pending claims which applicant considers to have been in possession of and fully enabled for prior to 7/17/01.

Formal Matters:

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claims 45-49 are objected to for lacking a period (".") following the claim numbers. Correction is required.

The deposit of biological organisms is considered by the Examiner to be necessary for enablement of the current invention (see MPEP Chapter 2400 and 37 C.F.R.§§1.801-1.809). Examiner acknowledges the deposit of organisms under accession number ATCC 209489 under terms of the Budapest Treaty on International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure in compliance with this requirement (see specification, page 250-251).

The information disclosure statement, paper number 5, has been considered.

Double Patenting:

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 39-44, 46-48, and 50-51 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending Application No. 09/903520. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to PRO335, which is 100% identical to SEQ ID NO: 294 from residue 20 to the terminus. Accordingly, PRO326 and PRO335 appear to differ only in their signal sequences, and the claims are coextensive.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Objections and Rejections under 35 U.S.C. §101 and 112:

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or

composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 39-51 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility.

The specification discloses a protein designated PRO326, and nucleic acid encoding such. At page 31 of the specification it is disclosed that PRO326 has (unspecified) homology to members of the leucine rich repeat superfamily. At page 110 it is stated that PRO335, 331 and 326 polypeptides "are related to LIG-1 and possess the biological functions of this family." However, what specific biological functions PRO326 possesses that are in common with LIG-1, and what uses that would indicate for PRO326 are not indicated. At page 138, it is stated "Uses for PRO335, PRO331 or PRO326 including uses in competitive assays with LIG-1, ALS and decorin *to determine their relative activities* (emphasis added)."

Utility must be in readily available form. In Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct,.1966), a process of producing a novel compound that was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be useful because the compound produced thereby was potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The instant claims are drawn to a protein which has undetermined function or biological significance. Until some actual and specific activity can be attributed to the protein identified in the specification as PRO326 protein, the claimed invention is incomplete. Merely using the protein to determine the properties thereof does not constitute a patentable utility.

It is further noted that PRO326 is disclosed as having given positive results in three assays. The first is found at pages 208-209 of the specification, and is described as a mixed lymphocyte reaction. The specification states that "any value greater than control indicates a stimulatory effect

for the test protein." This assay is not considered to impart utility to the protein PRO326, nor to the nucleic acids that encode it. The reason for this determination is that no results are presented, and the standard disclosed, "any value greater than control", is not considered to be an acceptable standard in the scientific community. It is well accepted in experimental science that, in order for a result to be positive, it must be *significantly* different from the control value, not "any value greater" as reported in the specification. Accordingly, the tacit assertion that PRO326 has a positive reaction in a mixed lymphocyte assay, and could therefore be used 'as a stimulator of the proliferation of stimulated T-lymphocytes" does not meet the requirements of 35 U.S.C. § 101, as the assertion of utility would not be considered substantial by a person of ordinary skill in the art.

The second assay in which PRO326 was stated to give positive results is found at pages 210-211, the skin vascular permeability assay (Assay 64). Presumably a positive reaction indicates that a measurable blemish was observed (though this is not clearly stated), and then biopsied, and one or more types of inflammatory cells were observed in the biopsy. This assay is not considered to be indicative of utility for PRO326, because it is merely what is commonly known as an immediate type hypersensitivity assay, and does not inform as to what the protein could be used for, especially in the absence of any information as to what *particular* cell types were observed in the biopsy. Thus, it is not clear what type of immune response was stimulated, nor what utility would stem from such. Again, the person of ordinary skill in the art would not find that this assay constitutes a specific, substantial and credible assertion of utility.

Finally, at pages 218-222 (Example 91), the specification discloses an in vitro antitumor assay (assay 161). The specification discloses, in Example 91, that the PRO326 protein was active, causing at least 50% growth inhibition, against four of the 60 cell lines of the National Cancer Institute (NCI) anticancer drug discovery screen (the NCI panel). The asserted utility of nucleic acids encoding the claimed PRO326 protein as a possible chemotherapeutic agent is not considered to be specific, substantial and credible, for the following reasons: Monks et al., Journal of the National Cancer Institute, vol. 83(11):757-766, cited by applicants at page 218, disclose and explain the screen itself, including how the screen is performed, and what cell lines are used. The 60 cell

lines are independent isolates representing seven distinct types of cancer, namely lung cancer (13 cell lines), renal cancer (9 cell lines), colon cancer (9 cell lines), melanoma (9 cell lines), CNS cancer (8 cell lines), ovarian cancer (6 cell lines), and leukemia (6 cell lines). The specification, at pages 218-222, discloses that PRO326 tested positive in 4 cell lines, representing three CNS, and one NSCL cancers. Based on disclosed results for other PRO polypeptides, other cell lines tested included a variety of cancer cell lines, including breast cancer cell lines. As the Monks et al. disclosure does not disclose any breast cancer cell lines as being in the panel, it is not clear exactly *which* "NCI panel" was used.. It is also noted that the composition of the NCI panel is not static, as Shi et al., referenced below, disclose a different set of 60 cell lines than that disclosed by Monks et al. It cannot be determined how many CNS and NCSL cancer cell lines were present in the panel used. Therefore, there is no discernable pattern of activity, i.e. the protein does not appear to be active against any particular type of cancer, nor against anything approaching a majority of the cell lines for any given type of cancer. Since PRO326 does not appear to give significant results when tested against the NCI panel, the implicit assertion of utility for the protein (and by extension nucleic acids encoding such) as an anti-cancer agent is not specific, as such could be asserted for almost any protein, which would be toxic for one or more cell types at some concentration. Further, the implicit assertion of anticancer activity is not substantial. Johnson et al. (Brit. J. Cancer 84(10):1424-1431), in an article entitled "Relationships between drug activity in NCI preclinical in vitro and in vivo models and early clinical trials", state, with regard to the NCI panel that "Agents selected on the basis of potency, selective activity against a particular disease category, and/or differential activity against a few specific cell lines were then evaluated against a small number of sensitive human tumors in the nude mouse xenograft model (citations omitted) as a basis for selecting compounds for further preclinical development. Owing to the large numbers of molecules emerging from the in vitro screen as candidates for xenograft testing, in 1995 this development path was further modified to include a hollow fibre (HF) assay, activity in which was a prerequisite for study in classical xenograft models" (page 1424, second column). Thus, the initial screen against the 60 cell lines of the NCI panel is not considered by the art to be predictive of *in vivo* activity against tumors,

and, as characterized by Johnson et al., such is merely the first of a three-part protocol for identification of agents to be tested in vivo. Further, Shi et al., (J. Chem. Inf. Comput. Sci. 40:367-379), clearly state that "Although cell growth inhibitory activity for a *single* cell line is not very informative, activity *patterns* across the 60 cell lines can provide incisive information on the mechanisms of action of screened compounds...." (abstract). The paper, drawn to methods of mining and visualizing the large amounts of data generated by the NCI panel, further states that relative activity levels distinguish better among the tested cell lines than do the GI_{50} activity patterns, and that "The mean zero preprocessing procedure seemed to eliminate the noninformative "inherent" cytotoxicity, thus brining out the informational differential cell responses (p. 377, end of first column). Thus, Shi et al. indicates that the art does not consider the raw GI_{50} data are insufficient to identify compounds that are likely to be antitumor candidates to be tested further. Accordingly, the implicit assertion of utility as an anti-cancer agent is not substantial, as the art does not support that mere identification of 50% killing of 4 of the 60 NCI panel cell lines would be predictive of anti-tumor activity, and thus would not constitute a substantial and credible utility for PRO326 and by extension nucleic acids encoding such.

In Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), a process of producing a novel compound that was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be useful because the compound produced thereby was potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The instant claims are drawn to a protein which has undetermined function or biological significance. Until some actual and specific activity can be attributed to the protein identified in the specification as PRO326 protein, the claimed invention is incomplete.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-51 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 39-43 and 50-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity with a particular disclosed sequence. The claims do not require that the protein possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides that are defined only by sequence identity.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the

structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 294, the extracellular domain thereof, or with or without the signal sequence, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Prior Art:

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

U.S. Patent Number 6,046,030 teaches a protein of SEQ ID NO: 5, having 50% identity to

residues 1-1083 of SEQ ID NO: 294.

U.S. Patent Number 6,426,072 teaches SEQ ID NO: 4, which has 74.8% identity to residues 608-737 of SEQ ID NO: 294.

A search of the protein sequence databases revealed the following prior art:

Locus	Date	Author	Identity to SEQ ID NO:294
Q9D332	6/1/01	J. Kawai et al.	86% to residues 378-1119
O94898	5/1/99	T. Nagase et al.	58.4% to residues 47-1036
P70193	2/1/97	Y. Suzuki et al.	50% to residues 1-1083

Advisory Information:

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 5:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary L. Kunz, at (703)308-4623.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 872-9306 (before final rejection) or (703)872-9307 (after final). Faxed draft or informal communications with the examiner should be directed to (703) 746-5228.

Lorraine Spector

Lorraine Spector, Ph.D.
Primary Examiner

09/945587.1
1/18/03